

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



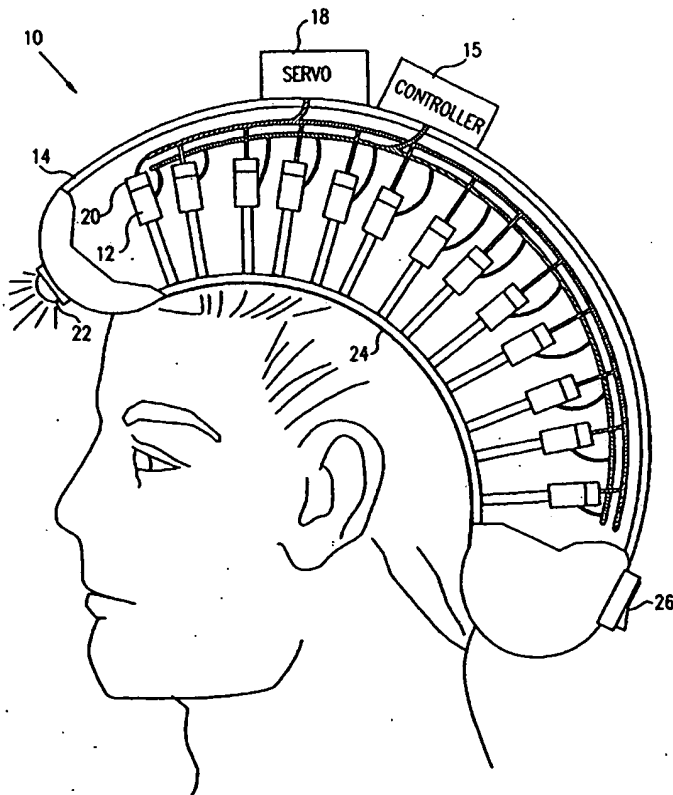
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|----|---|
| (51) International Patent Classification ⁶ : A61N 5/06 | | A1 | (11) International Publication Number: WO 99/62599 |
| | | | (43) International Publication Date: 9 December 1999 (09.12.99) |
| (21) International Application Number: PCT/IL99/00287 (22) International Filing Date: 31 May 1999 (31.05.99) (30) Priority Data: 124722 2 June 1998 (02.06.98) IL (71)(72) Applicant and Inventor: ORON, Amir (IL/IL); David Pais Street 11, 75260 Rishon le Zion (IL). (74) Agents: COLB, Sanford, T. et al.; Sanford T. Colb & Co., P.O. Box 2273, 76122 Rehovot (IL). | | | (81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). |
| | | | Published With international search report. |

(54) Title: ISCHEMIA LASER TREATMENT

(57) Abstract

Apparatus (10) for treatment of an ischemic region of brain cells in a cranium, comprising a skull covering (14) adapted to cover at least part of the cranium, at least one guide (16) attached to the skull covering (14), and a laser source (12) which is operative to direct a laser beam through the at least one guide (16) into the cranium. The at least one guide may include an optic fiber or a waveguide.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakhstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LJ | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

FIELD OF INVENTION

Cytoprotective effect and increase of survival of neurons in the Central Nervous System (CNS) of mammals following ischemia (as in stroke), by low energy laser (LEL) irradiation.

BACKGROUND OF THE INVENTION

Mammalian CNS neurons have a negligible capacity to regenerate following lesion or acute ischemic (no oxygen supply) conditions. A dramatic decrease or complete abolishment of oxygen supply to the nerve cells and other cells in a certain region of the brain can occur due to occlusion of one or more of the arteries that supply blood to the brain (*Fisher M.*, "Characterizing the Target of Acute Stroke Therapy", *Stroke*, Vol. 28 No 4 pp. 866-872, April 1997). Concomitantly with this event, the neurons of the brain go through a gradual degeneration process that eventually leads to necrosis in the acute ischemic zone. Clinical syndromes such as paraplegia, quadriplegia, etc., are evident due to dysfunction of the nerve cells in the brain.

The mammalian CNS also has a negligible capacity to regenerate following injury. Limited regeneration of peripheral axons in mammals and CNS in lower vertebrate can take place in a post trauma setting.

Low energy laser irradiation has recently been found to modulate various processes in different biological systems, (*Belkin et al*, A critical review of low energy laser bioeffects. *Lasers Light Ophthalmology* vol. 2 p. 63-71, 1988 and *Conlan et al*, Biostimulation of wound healing by low energy laser irradiation, *Journal of Clinical Periodontology* vol. 23, p. 492-496, 1996). The effect of low energy laser irradiation following trauma has been investigated so far in skin, peripheral nerves and skeletal muscles.

Assia et al (Temporal parameters of low energy laser irradiation for optimal delay of post traumatic degeneration of Ito rat optic nerve, *Brain Research* 476: 205-212, 1989) described the possibility of delaying the post traumatic process of degeneration and scar tissue formation of a crushed optic nerve (peripheral nervous system) by low energy laser irradiation.

U.S. Patent No. 5,580,555 to *Schwartz* involves the administration of tumor necrosis factor (TNF) to the sight of injury in the optic nerve in order to facilitate regeneration of axons across the sight of the injury. The use of low energy laser in conjunction with the use of the TNF is suggested to augment the effect of TNF. However, *Schwartz* presents no experimental

results to favor the beneficial effect of the laser. Furthermore, it is described in the detailed description that treatment with TNF alone (without laser irradiation) gives good results.

It has previously been suggested that regeneration of injured peripheral nerves can be accelerated by LEL (*Rochkind S.* Stimulation effect of laser energy on the regeneration of traumatically injured peripheral nerves. The Krim National Medical Inst., Morphogenesis and Regenerations Vol. 73: pp. 48-50, 1978). *Nissan M., Rochkind S. et al* (HeNe laser irradiation delivered transcutaneously: its effect on sciatic nerve of rats. *Laser. Surg. Med.* Vol. 6: pp. 435-438, 1986) also demonstrated that transcutaneous LEL of sciatic nerve induced an increase in the amplitude of the electrical signals recorded in the irradiated nerve, i.e. increased the size of the action potential.

U.S. Patent No. 4,966,144 to *Rochkind et al.* deals with a method of inducing functional regeneration of nerve fibers of an injured sight of the spinal cord (or using grafts of peripheral nerves which were placed into the injured sight) by a light source which generates light at a wavelength of 330-1200 nm. The method involves only the spinal cord but not the brain. Moreover, the method is not related to an acute ischemic phase of nerve cells in the CNS as in a situation of "stroke" nor is the cytoprotective effect of laser irradiation cited in *Rochkind et al.*

It has previously been reported that the low energy laser irradiation causes a decrease in the inflammatory response following injury to skeletal muscles (*Bibikova A. & U. Oron.* Promotion of muscle regeneration following cold injury to the toad (*Bufo Viridis*) gastrocnemius muscle by low energy laser irradiation. *Anat. Rec.* (1993) vol. 235 pp. 374-380 and *N. Weiss & U. Oron* Enhancement of muscle regeneration in the rat gastrocnemius muscle by low energy laser irradiation. *Anat. Embryol.* (1992) Vol. 186 pp. 497-503). The above phenomenon may suggest possible cytoprotective effect of at least the mitochondria and maybe other structures of the cell by the LEL. Thus, LEL irradiation allows cells under stressful conditions of low or no oxygen supply to maintain their viability in spite of the harsh conditions. The irradiated cells most probably do not degenerate to the same extent as the non-irradiated cells and therefore also the inflammatory response, which is typical to tissues undergoing a degenerative process following injury, is markedly decreased. Furthermore, LEL irradiation has been found to enhance the process of formation of new blood vessels (angiogenesis) in injured skeletal muscles (*Bibikova A, Belkin A. and Oron U.* Enhancement of angiogenesis in regenerating gastrocnemius muscle of the toad (*Bufo Viridis*) by low energy laser irradiation. *Anat. Embryol.* (1994) Vol. 190 pp. 597-602).

So far, despite significant research efforts for many years worldwide, a safe and effective method of inhibiting or eliminating the adverse irreversible effects of stroke and other ischemic events on brain cells and the significant clinical manifestations of it on animal and human body function has yet to be developed.

5

SUMMARY OF THE INVENTION

The present invention seeks to provide a novel method and apparatus for using LEL irradiation to protect cells under acute ischemic conditions in the brain. In accordance with the present invention, in the initial phase of ischemia, the LEL irradiation causes an enhanced angiogenesis process which in turn causes a regeneration process in the injured brain cells in the ischemic zone, thereby allowing for greater protection of the cells in the future.

10

There is thus provided in accordance with a preferred embodiment of the present invention apparatus for treatment of an ischemic region of brain cells in a cranium, including a skull covering adapted to cover at least part of a cranium, at least one guide attached to the skull covering, and a laser source which is operative to direct a laser beam through the at least one guide into a cranium. The at least one guide may include an optic fiber or a waveguide.

15

In accordance with a preferred embodiment of the present invention the laser source includes a diode laser.

20

Further in accordance with a preferred embodiment of the present invention a laser controller is operatively connected to the laser source which controls operation of the laser source.

Still further in accordance with a preferred embodiment of the present invention an actuator which is operative to move the laser source further from or closer to a cranium.

Additionally in accordance with a preferred embodiment of the present invention the skull covering includes sealing material at a skull-contacting periphery thereof.

25

In accordance with a preferred embodiment of the present invention a timer is mounted on the skull covering.

Further in accordance with a preferred embodiment of the present invention an indicator light is mounted on the skull covering.

30

Still further in accordance with a preferred embodiment of the present invention a plurality of the guides are attached to the skull covering which direct a plurality of the laser beams in a plurality of directions.

Additionally in accordance with a preferred embodiment of the present invention a plurality of the guides are attached to the skull covering which are operative to focus a plurality of the laser beams in a plurality of focal lengths into a cranium.

5 In accordance with a preferred embodiment of the present invention a plurality of the guides are commonly attached to the laser source.

Further in accordance with a preferred embodiment of the present invention a plurality of the laser sources and a plurality of the guides are provided, wherein each source directs a laser beam through one the guide.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The present invention will be understood and appreciated more fully from the following detailed description, taken in conjunction with the drawings in which:

Fig. 1 is a simplified pictorial illustration of apparatus for treatment of an ischemic region of brain cells in a cranium, constructed and operative in accordance with a preferred embodiment of the present invention;

15 Fig. 2 is a simplified pictorial illustration of apparatus for treatment of an ischemic region of brain cells in a cranium, constructed and operative in accordance with another preferred embodiment of the present invention; and

Fig. 3 is a simplified pictorial illustration of apparatus for treatment of an ischemic region of brain cells in a cranium, constructed and operative in accordance with yet another preferred embodiment of the present invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Reference is now made to Fig. 1 which illustrates apparatus 10 for treatment of an ischemic region of brain cells in a cranium, in accordance with a preferred embodiment of the present invention.

25 Apparatus 10 preferably includes a multiplicity of laser sources 12, such as diode lasers, arranged for multidirectional multifocal irradiation of the cranium. Laser sources 12 are mounted in a skull covering 14, preferably constructed of metal, plastic or any other irradiation blocking material, and are preferably controlled by a laser controller 15, either mounted externally or internally on skull covering 14. Each laser source 12 preferably delivers laser energy to the skull via a guide 16, such as an optic fiber or waveguide. Laser sources 12 are preferably connected to a servo system 18 which includes one or more actuators 20 which can move laser sources further from or closer to the cranium, thereby controlling the distance of the distal ends of guides 16 from the cranium.

Skull covering 14 may cover the entire skull including the brainstem, or alternatively, only part of the skull. Apparatus 10 preferably includes one or more indicator lights 22 which provide various operational visual signals, such as malfunction warning signals, for example. Skull covering 14 preferably has sealing material 24 at its skull-contacting periphery so as to prevent stray radiation from escaping. Apparatus 10 preferably includes a timer 26 with an LCD to allow an operator to monitor the irradiation process in real time. Other safety options may be included.

Reference is now made to Fig. 2 which illustrates apparatus 30 for treatment of an ischemic region of brain cells in a cranium, in accordance with another preferred embodiment of the present invention. Apparatus 30 is basically the same as apparatus 10, with like numerals designating like elements, although not all elements are shown in Fig. 2 for the sake of simplicity. Apparatus 30 differs from apparatus 10 in that apparatus 30 includes one laser source 12 and a multiplicity of guides 16 which are arranged for multidirectional multifocal irradiation of the cranium, as described above for apparatus 10.

Reference is now made to Fig. 3 which illustrates apparatus 40 for treatment of an ischemic region of brain cells in a cranium, in accordance with yet another preferred embodiment of the present invention. Apparatus 40 is basically the same as apparatus 10 or 30, with like numerals designating like elements, although not all elements are shown in Fig. 3 for the sake of simplicity. Apparatus 40 differs from apparatus 10 or 30 in that apparatus 40 also includes a heartbeat sensor probe 42. Guide 16 may be housed inside or outside of probe 42, in accordance with the requirements of the particular application. Apparatus 40 is particularly useful for treating newborn infants, as is now described.

During the process of birth, a newborn may be subject to different kinds of stress-related problems, one example being insufficient oxygen and blood supply to the brain which is a major cause of morbidity and mortality. Factors contributing to brain damage and other adverse outcomes are complex. Both severe hypoxia-ischemia and prolonged hypoxia of lesser severity may cause brain damage (*Low JA, Cerebral perfusion, metabolism and outcome; Curr Opin Pediatr*: 7(2): pp. 132-9 Apr 1995). Many morbid conditions are associated with hypoxia such as hypoxic-ischemic encephalopathy, cerebral palsy, microcephaly, seizure disorders, mental retardation, educational failure and others (*Behrman, Kliegman et al, Nelson's Textbook of Pediatrics*, 15th Ed. W.B.Saunders Company: pp. 431-3; 1996).

Apparatus 40 is particularly useful for treating newborns, such as during exit from the vagina, wherein laser sources 12 can deliver laser energy to the cranium of the newborn infant

quickly and efficiently. In such use for newborns, apparatus 40 may be fashioned without skull covering 14, if desired. Alternatively, an assortment of skull coverings 14 of different sizes and shapes may be provided to a hospital or clinic for perinatal care. Different energy delivery coefficients may be calculated for laser sources 12 depending upon the particular application.

- 5 The position of the laser sources and the paths of the laser beams into the cranium are based on various factors, such as an anatomical consideration of the newborn (for example, the anatomy of the fontanel).

Apparatus 40 can be combined with conventional monitoring systems and with those under current development. The technique of irradiating the brain with apparatus 40 may be used in conjunction with other methods for protecting the brain, such as the use of glutamate receptor antagonists, glucocorticoids, voltage sensitive calcium channel antagonists etc. (*Tuor UI, Del Bigio MR et al, Brain damage due to cerebral hypoxia/ischemia in the neonate: pathology and pharmacological modification; Cerebrovasc Brain Metab Rev, 8(2): pp 159-93 Summer 1996*).

- 15 The invention was carried out using the above-described apparatus in two exemplary experiments which are now described.

Experiment I:

The left common carotid artery of 12 mature Sprague-Dawley rats (250-300 gr. body weight anesthetized with Avertin) was exposed by a longitudinal incision to the frontal midline section of the neck. It was then occluded by ligation with a silk (4-0) thread.

20 The brains of six rats were irradiated by a diode laser. The irradiation was performed by a longitudinal incision in the scalp to expose the skull. The laser source (wavelength 807 millimicron, 400 mW maximal power output) was attached to the parietal bone in the skull (after exposing the skin) at two points: one between the eyes and one 1 cm posterior to the previous one. The duration of each irradiation was 2 minutes. The dispersion of the laser beam after its passage through the skull was measured by an infrared viewer in a preliminary experiment. The energy density that reached the brain tissue was 8 mW per square centimeter. The other six rats had lasers attached to the skull but the lasers were not connected to an energy source

- 30 Rats were followed up after surgery for various neurological disorders. All the rats that did not receive laser irradiation showed a prolapsed eyelid on the left side and minor motor neurological deficits at 12 hours post occlusion of the left carotid artery.

The six rats that were irradiated as above revealed the following:

One had a prolapsed eyelid on the left side with no other symptoms. all other rats- revealed neither eyelid prolapse nor any neurological deficits.

Experiment II:

5 Occlusion of the left coronary artery was performed on fifteen white mice (25-35 gr.) in a similar method to that described for rats in Experiment I.

Seven of the mice were irradiated with the same laser as in experiment I. The irradiation was performed through the skin that covers the skull. The power output of the laser was set so that the brain of the mice was exposed to an energy of 5 mW/sq. cm. for 2 minutes.

10 Since the laser beam beyond the skull was dispersed to a diameter of approximately 1.5 cm, only one irradiation in the center of the parietal bone was performed. The irradiation covered the entire dorsal part of the brain.

The other 8 mice served as control animals which went through the same process as the laser irradiated mice, but with the laser not turned on.

15 After induction of the stroke by ligation of the carotid artery, the mice were observed daily for neurological disorders/ deficits and loss of weight. The results are presented in Table I.

It can be seen from Table I that neurological deficits such as prolapse of the left eyelid and paresis of hind legs (which was also evident by difficulty in locomotion) was significantly
20 higher in the control non-irradiated mice. Furthermore, in 7 out of the 8 non-irradiated mice examined, the ligation of the left carotid artery resulted in up to 50% loss of weight and eventual death. In none of the laser irradiated mice was there a massive weight loss nor did any of them die due to the ligation of the left carotid artery.

It is therefore concluded that laser irradiation most probably has a protective effect on
25 the nerve cells of the CNS or some other protective effect on the CNS as a whole unit. This effect inhibited adverse consequences that usually led to death in this experimental model. It may be postulated that the same protective effect may also be beneficial in the case of stroke or other ischemic events in the CNS of humans.

Table I: Effect of Laser Irradiation on mice post ligation of the Left Common Carotid Artery.

| Treatment | Death up to 10 days post ligation. | Paresis in hind legs. | Prolapse of left eyelid. | Significant loss of weight. |
|--------------------------|------------------------------------|-----------------------|--------------------------|-----------------------------|
| Control (non irradiated) | 7/8 | 6/8 | 6/8 | 7/8 |
| Laser irradiated | 0/7 | 0/7 | 1/7 | 0/7 |

In addition to the above experiments, penetration of low energy laser irradiation through a human skull was studied using a fresh human skull. A Ga-As diode laser was applied (800 mW maximal output) and a laser meter was placed in the inner side of the skull cavity in order to detect the energy power and dispersion (using a laser infrared viewer) of the laser after penetration through the skull. The beam diameter of the laser was dispersed from 2 mm externally to the skull to 3.5 cm in the skull cavity after penetration through the skull wall in the parietal region of the skull (a width of about 8 mm). The energy density measured inside the skull cavity was 3 mW/sq.cm. In the squamosal region (side region) of the human skull the width of the skull is about 5 mm, so it can be expected that penetration of the laser energy should be better.

The above study shows that the human skull can serve as a "natural lens" that disperses the laser beam so that a larger area of the brain will be laser irradiated. The penetration of low energy laser through the human skull is a feasible option to deliver this energy to the brain cells if the external laser source is operated at the proper power output. This energy will cause a beneficial biostimulation on brain cells after stroke and other related disorders.

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of the features described hereinabove as well as modifications and variations thereof which would occur to a person of skill in the art upon reading the foregoing description and which are not in the prior art.

What is claimed is:

1. Apparatus for treatment of an ischemic region of brain cells in a cranium, comprising:
a skull covering adapted to cover at least part of a cranium;
5 at least one guide attached to said skull covering; and
a laser source which is operative to direct a laser beam through said at least one guide into a cranium.
2. Apparatus according to claim 1 wherein said at least one guide comprises an optic fiber.
- 10 3. Apparatus according to claim 1 wherein said at least one guide comprises a waveguide.
4. Apparatus according to claim 1 wherein said laser source comprises a diode laser.
5. Apparatus according to any of the preceding claims further comprising a laser controller operatively connected to said laser source which controls operation of said laser source.
- 15 6. Apparatus according to any of the preceding claims further comprising an actuator which is operative to move said laser source further from or closer to a cranium.
7. Apparatus according to any of the preceding claims wherein said skull covering comprises sealing material at a skull-contacting periphery thereof.
8. Apparatus according to any of the preceding claims further comprising a timer mounted
20 on said skull covering.
9. Apparatus according to any of the preceding claims further comprising an indicator light mounted on said skull covering.
10. Apparatus according to any of the preceding claims further comprising a plurality of said guides attached to said skull covering which direct a plurality of the laser beams in a
25 plurality of directions.
11. Apparatus according to any of the preceding claims further comprising a plurality of said guides attached to said skull covering which are operative to focus a plurality of the laser beams in a plurality of focal lengths into a cranium.
12. Apparatus according to claim 1 further comprising a plurality of said guides which are
30 commonly attached to said laser source.
13. Apparatus according to claim 1 further comprising a plurality of said laser sources and a plurality of said guides, wherein each source directs a laser beam through one said guide.

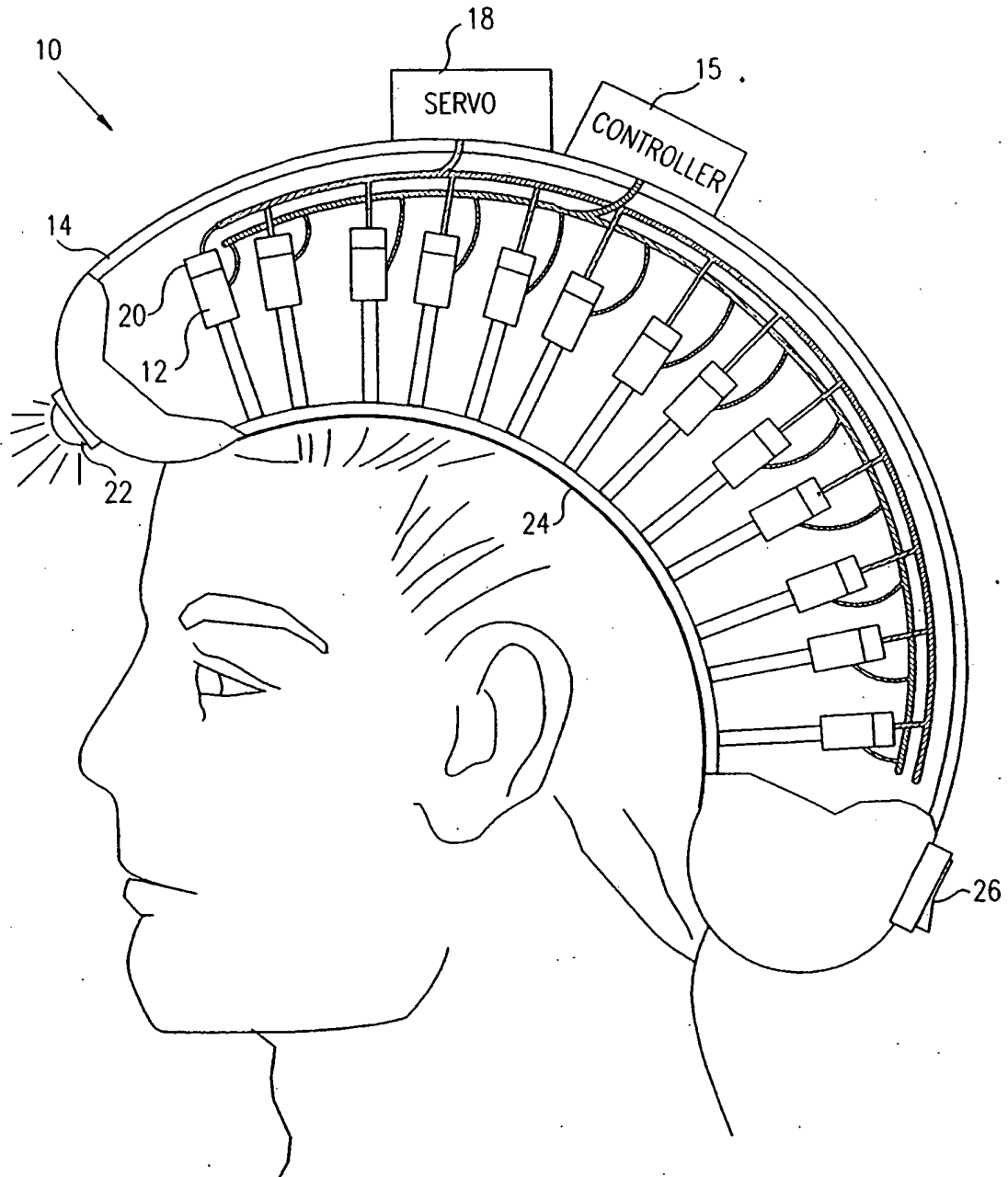


FIG. 1

2/2

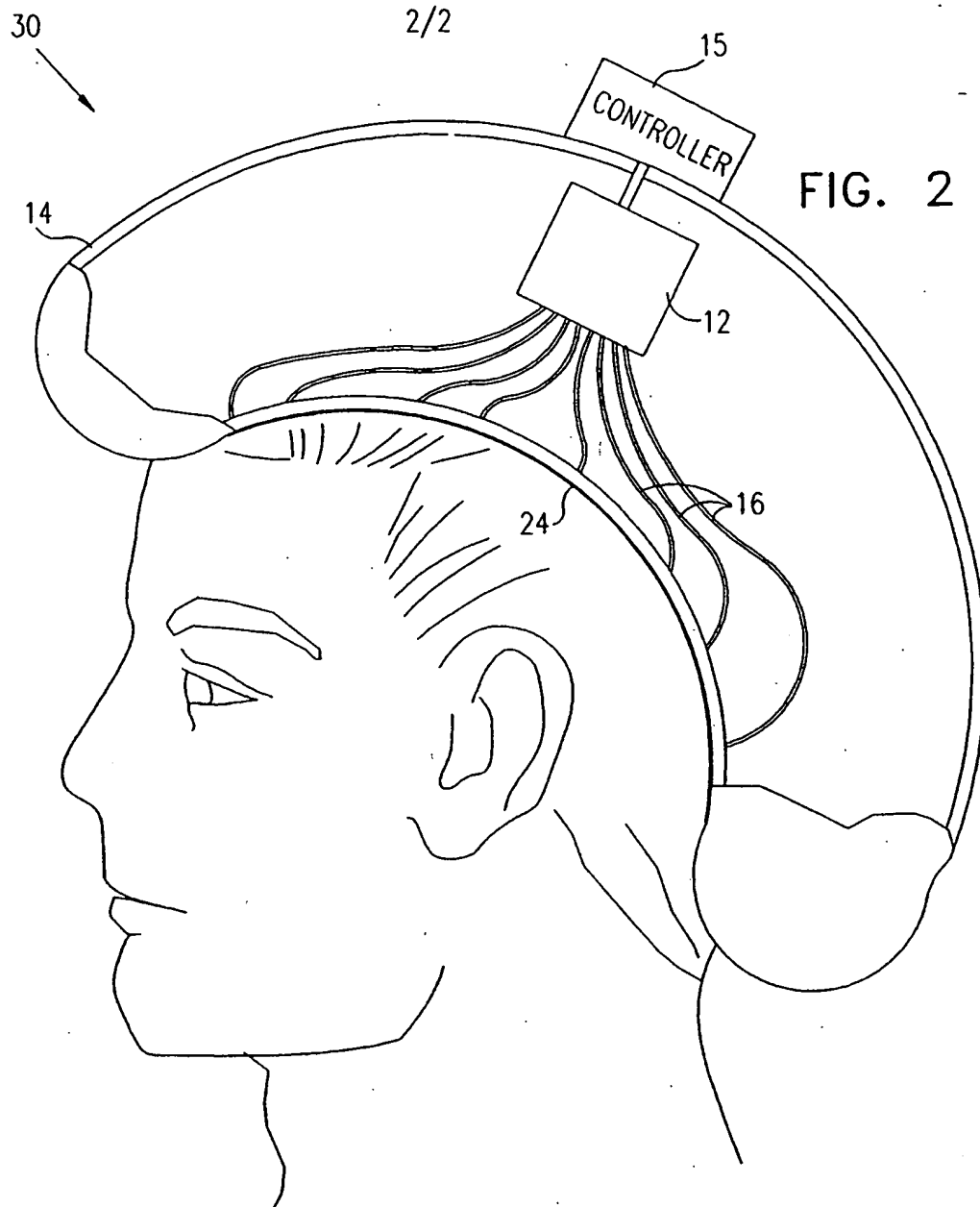


FIG. 2

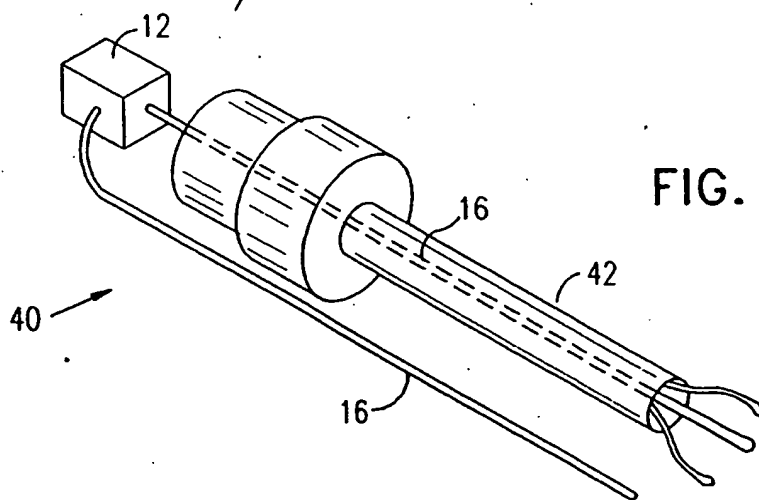


FIG. 3

INTERNATIONAL SEARCH REPORT

Inter nat Application No

PCT/IL 99/00287

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61N5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP 0 130 950 A (TESSIORE ADRIANO) 9 January 1985 (1985-01-09) the whole document ---- | 1-5,8-13 |
| X | US 5 616 140 A (PRESCOTT MARVIN) 1 April 1997 (1997-04-01) column 1, line 29 - line 44 column 12, line 26 - line 41; figure 7 ---- | 1,4,5 |
| A | US 4 966 144 A (ROCHKIND SIMEONE ET AL) 30 October 1990 (1990-10-30) cited in the application column 2, line 34 - column 3, line 34 ----- | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

3 September 1999

Date of mailing of the international search report

13/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Fax: (+31-70) 340-3016

Authorized officer

Petter, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 99/00287

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|------------------------------|--------------------------|
| EP 0130950 A | 09-01-1985 | IT 1171078 B AT 51760 T | 10-06-1987 15-04-1990 |
| US 5616140 A | 01-04-1997 | AU 2104195 A WO 9525563 A | 09-10-1995 28-09-1995 |
| US 4966144 A | 30-10-1990 | NONE | |